Increased incidence of cancer in the follow-up of obstetric antiphospholipid syndrome within the NOH-APS cohort

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Statistical analysis

The quantitative variables were described by median, interquartile range and range values, and the qualitative variables were described by numbers and percentages.

The outcome analysis of the follow-up period was performed in the intention-to-treat population, which included all patients according to the group to which they belonged.

We calculated the time-to-event from the date of enrollment to the date of the diagnosis in patients with an incident cancer during follow-up, or to the date of death in patients who died with no cancer diagnosis during follow-up, or to the date of the last annual assessment in patients lost to follow-up, or to the date of the annual consultation of 2017 in patients with no cancer diagnosis. We estimated the rate of incident cancer as the number of cancer diagnoses during the observation period divided by the total number of person-years of observation, with the corresponding 95% confidence intervals (CI) for these rate estimates. Log-rank tests were used to compare Kaplan-Meier estimates for cancer-free curves in the three groups in a time-to-first-event analysis. Hazard ratios (HR) and 95% confidence intervals (95%CI) were estimated with the use of a Cox-proportional-hazards model. For between-group comparisons, nominal two-sided P values of 0.05 or less were considered to indicate statistical significance. For the primary endpoint, we performed an unadjusted analysis (the main analysis). For multivariate models, and because not all confounders were known for our study's model, a backward elimination was performed, starting with a full predefined model, with variables selected on the basis of previous known associations or scientific interest, with adjustment being finally performed for all variables with $P < 0.20$ in the multivariate models. The final model included only main effects with $P < 0.05$. The full predefined model included variables at inclusion (age, body mass index, type of PL, primary/secondary PL) and variables during follow-up (family history of cancer, family

history of venous thromboembolism, family history of atherothrombosis, active smoking, non-cancerous inflammatory disease, immunosuppressive treatments, diabetes mellitus, PL and type of PL after inclusion, stillbirth, placenta-mediated complications -pre-eclampsia, HELLP syndrome, placental abruption, birth of a small-for-gestational age SGA neonate-, neonatal death, venous thromboembolism- as a whole, then pulmonary embolism, proximal deep vein thrombosis and distal deep vein thrombosis-, superficial vein thrombosis, arterial thrombosis), all variables and clinical events being defined as previously described [6, 7-10]).

We calculated standardized incidence ratios (SIRs), defined as the [observed cases : expected cases] ratios, using the indirect method according to Breslow and Day [11]. The expected number of cancer cases in our cohort was extrapolated from the age-specific rates observed in women in the local population-derived registry of tumors in Montpellier area (Registre des Tumeurs de l'hérault: [7]), which covers one million inhabitants.

Finally focusing on the oAPS group, we studied the association between incident cancers and aPL Abs. Each of the 5 aPL Abs had been checked during each annual assessment, being negative or positive, each positivity being associated with an antibody titre as previously described [6] (briefly: aCL and aβ2GP1 antibodies: according to calibration curves using the Sapporo standards HCAL and EY2C9, results in µg/ml; LA: quantification using the results of the mixing test, finally expressed as the ratio of the aPTT test result from the patient and healthy pooled plasma mixed 1:1, divided by the aPTT test result from the healthy pooled plasma; PTT LA® reagent, Stago, Asnières France). We studied first the association with the type of positive aPL Ab at inclusion, second with the cumulative "exposure" (E: defined as the sum of the all positivities during the whole follow-up) to each at least one time positive aPL Abs during follow up (E^{LA}, $E^{aCL\text{-}G}$, $E^{aCL\text{-}M}$, $E^{a\beta2GP1\text{-}G}$, $E^{a\beta2GP1\text{-}M}$) , third with the cumulative "intensity of exposure" (IE: defined as the sum of the corresponding

positive antibody titres) to each at least one time positive aPL Abs during follow (intensity meaning strength of the positive antibody titre; (IE^{LA}, $IE^{aCL\text{-}G}$, $IE^{aCL\text{-}M}$, $IE^{a\beta2GP1\text{-}G}$, $IE^{a\beta2GP1\text{-}M}$). For each aPL Ab, E was defined as the sum of the all positivities during the whole follow-up, and IE as the sum of the corresponding positive antibody titres. The variables (aPL Abs, Es, EIs) potentially linked to cancer were introduced into a multiparametric logistic model, adjustment being also performed on age at inclusion.

This was an observational study based on our recruitment capacities over a 10-year period. We did not, therefore, perform sample size calculations before the study. However, assuming a 0.05 □ level and a 0.80 (1-β) level, and an unilateral testing, the theoretical proportion of incident cancers (expected cases diagnosed according to our observational conditions) being extrapolated from the registry of tumors in Montpellier area, the ability to detect a cancer incidence multiplied by 1.5 requires 1613 patients, multiplied by 1.75: 912 patients, multiplied by 1.8: 746 patients, by 1.9: 594 patients and by 2: 422 patients.

Statistical analyses were performed using StatView®-windows software version 5.0 (SAS Institute Inc., Cary, NC, USA), XLSTAT® software version 2015.4.01.20116 (Addinsoft SARL, Paris, France).